

## REVIEW ARTICLE

# The Challenge of Managing Atopic Dermatitis in the United States

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**BACKGROUND:** Atopic dermatitis is a chronic inflammatory skin disease that affects up to 13% of children and 10% of adults in the United States. Among patients and their families, atopic dermatitis has a considerable effect on quality of life and represents a substantial economic burden.

**OBJECTIVES:** To describe the impact and challenges of atopic dermatitis and to provide nondermatologists in the healthcare community an enhanced understanding of atopic dermatitis to facilitate treatment and pharmacy benefit discussions.

**DISCUSSION:** Atopic dermatitis is a heterogeneous disease, and its diagnosis is hampered by a lack of objective diagnostic criteria. The current management guidelines address the distinct clinical phenotypes as a single disease and do not incorporate recent clinical advances, such as the targeting of specific inflammatory processes. The treatment guidelines for atopic dermatitis are complex and challenge healthcare providers, patients, and caregivers. Novel treatments can provide additional therapeutic options for patients with atopic dermatitis.

**CONCLUSIONS:** Treatment options for atopic dermatitis are expanding with the development of novel anti-inflammatory therapies. An increased understanding of these advancements is necessary to optimize care for patients with atopic dermatitis.

**KEY WORDS:** anti-inflammatory therapies, atopic dermatitis, dermatology, economic impact, financial burden, medication adherence, quality of life, steroid phobia, topical calcineurin inhibitors, topical corticosteroids, treatment guidelines

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Atopic dermatitis is a chronic inflammatory skin disease that is characterized by intense itch and acute, subacute, or chronic eczematous skin lesions.<sup>1</sup> The disease course can be chronic or relapsing-remitting. Lesions typically present with an age-related morphology and distribution.<sup>1</sup> The prevalence of atopic

dermatitis is high, affecting up to 13% of children and 4% to 10% of adults in the United States.<sup>2-4</sup> The burden of atopic dermatitis on the quality of life (QOL) of patients and their families is substantial, encompassing physical and psychological well-being, social functioning, and economic costs.<sup>5</sup>

The pathophysiology of atopic dermatitis is complex and involves genetic susceptibility, environmental factors, microbiome effects, and immune dysregulation.<sup>6</sup> Traditional treatments for atopic dermatitis include the use of moisturizers to improve barrier integrity; topical anti-inflammatory medications when good skin care (such as bathing and moisturizing) is inadequate; and phototherapy, systemic immunosuppressants, or short-course systemic corticosteroids for recalcitrant or severe disease.<sup>7</sup> Impaired barrier function, which permits irritants to penetrate the skin surface and affects the local microbiome, is caused by the disease and may also contribute to the disease.<sup>8</sup> The recent development and approval of several new classes of medication for the treatment of atopic dermatitis has added variety to the treatment landscape.<sup>9-11</sup>

The objective of this article is to describe the current diagnostic criteria, treatment landscape, and burden of

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## KEY POINTS

- Atopic dermatitis is a chronic condition associated with a substantial impact on a patient's quality of life and has a considerable economic burden.
- A recent American Academy of Allergy, Asthma & Immunology consensus statement discusses emerging therapies and highlight the systemic nature of this disease.
- Traditional treatment regimens for atopic dermatitis are often complex and limited in their efficacy, tolerability, and safety.
- As in many chronic diseases, poor medication adherence is a concern; compared with topical therapies, oral or injectable options may help to improve adherence.
- Newer treatments are focused on specific anti-inflammatory pathways; the introduction of biologic agents may further help to improve patient outcomes.
- The approval of 2 novel medications in the past 2 years may revitalize the treatment landscape for atopic dermatitis.

atopic dermatitis to highlight the challenges that this disease presents to the wider healthcare community.

## Diagnosis of Atopic Dermatitis

There is no objective test to confirm a diagnosis of atopic dermatitis, and clinicians diagnose the disease based on the patient's clinical features and historical characteristics.<sup>1,12</sup> Diagnostic criteria are included in the atopic dermatitis practice parameters from the American Academy of Dermatology (AAD)<sup>1</sup> and the Joint Task Force on Practice Parameters of the American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy, Asthma & Immunology (ACAAI).<sup>12</sup> According to both guidelines, the essential features of atopic dermatitis include pruritus and chronic or relapsing eczematous lesions that present with age-related typical morphology and distribution.<sup>1,12</sup>

A history of allergic diseases or immunoglobulin (Ig) E reactivity (ie, atopy) is considered essential to the diagnosis of atopic dermatitis by the AAAAI/ACAAI guidelines and an important feature by the AAD guidelines.<sup>1,12</sup> These guidelines agree that a firm diagnosis of atopic dermatitis requires the exclusion of other skin conditions that have a similar appearance,<sup>1,12</sup> such as other inflammatory skin conditions (eg, seborrheic dermatitis, psoriasis, contact dermatitis), infections (eg, impetigo, molluscum dermatitis, candidiasis), and condi-

tions including scabies, keratosis pilaris, and ichthyosis vulgaris.<sup>13</sup> A number of rare disorders can also mimic atopic dermatitis, including Letterer-Siwe disease, cutaneous T-cell lymphoma, X-linked recessive ichthyosis, lamellar ichthyosis, IgA or IgM deficiency, and graft-versus-host disease.<sup>13</sup>

Although atopic dermatitis is historically considered a pediatric disease, with approximately 50% of individuals having symptoms within the first year of life and 95% of patients with disease onset at age under 5 years,<sup>14</sup> the prevalence of atopic dermatitis is considerable in adults (approximately 4%-10% globally).<sup>2,4</sup>

The morphology of atopic dermatitis varies, depending on the age of the patient (**Figure 1**).<sup>8,15</sup> In infantile atopic dermatitis (aged 3 months-2 years), lesions are acute and appear mainly on the face, extensor surfaces of the limbs, and trunk.<sup>8</sup> Childhood atopic dermatitis (aged 2-12 years) is characterized by acute and chronic lesions that appear primarily at the flexural folds and periorificial areas. In adolescents or adults (aged >12-60 years), atopic dermatitis is characterized by chronic lichenified (ie, thickened) or excoriated lesions that occur in typical areas, such as the head, neck, and flexural areas, but it can also affect the hands and periorbital areas. Finally, in older (aged >60 years) patients, atopic dermatitis is characterized by extensive lesions with a strong pruritic component that often spare flexural areas.<sup>8</sup>

In addition to age-specific phenotypes, the range of atopic dermatitis severity is wide.<sup>15</sup> Many disease severity scoring tools (such as the Eczema Area and Severity Index and Investigator's Global Assessment) do not assess the impact of atopic dermatitis on patient QOL, which is measured using other scales (such as the Dermatology Life Quality Index and Skindex).<sup>16</sup> Although these scoring tools are used frequently in clinical trials, their use in daily practice is still limited.<sup>15,16</sup> There is a discrepancy in the way patients and physicians rate the severity of atopic dermatitis, with physicians focusing primarily on sleep disturbance and patients focusing more on skin-related QOL.<sup>17</sup>

## Treatments for Atopic Dermatitis

Despite the heterogeneity of the clinical phenotype of atopic dermatitis, this condition is largely considered a single disease and is usually treated as such.<sup>15</sup> The AAD, AAAAI/ACAAI, and consensus European treatment guidelines recommend a stepwise approach that depends on disease severity.<sup>12,18-22</sup> Basic treatment for atopic dermatitis involves the use of moisturizers to improve the skin's hydration and barrier function. Topical anti-inflammatory medications, such as topical corticosteroids and topical calcineurin inhibitors, are used to treat flares or as maintenance therapy, whereas phototherapy,

**Figure 1** Typical Presentation of Atopic Dermatitis at Various Ages



A. Infantile atopic dermatitis is generally acute, with lesions on the face and extensor surfaces of the limbs.  
 B. From age 1-2 and older, polymorphous manifestations with various skin lesion types are seen, particularly in flexural folds.  
 C. Adolescents and adults often present with lichenified and excoriated plaques at flexures, wrists, ankles, and eyelids, and adults might only have chronic hand eczema or prurigo-like lesions.  
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systemic immunosuppressants, and systemic corticosteroids are recommended for recalcitrant or severe disease.<sup>12,18-22</sup>

The guidelines provide detailed and largely comparable treatment recommendations with a common goal of maintaining the skin barrier, reducing the inflammatory

response, and eliminating atopic dermatitis triggers<sup>23</sup>; however, these recommendations have several limitations. The most recent AAD and AAAAI/ACAAI guidelines were published approximately 10 years after the previous publication of guidelines, which necessitat-

ed the inclusion of a decade's worth of therapeutic and scientific advances.<sup>7</sup> The process of updating the guidelines, however, does not allow for the timely incorporation of novel therapies.<sup>16</sup> The guidelines are extensive, which is problematic for primary care physicians who need more accessible information.<sup>7</sup>

A number of changes to the treatment paradigm have occurred since the publication of the AAD and AAAAI/ACAAI guidelines in 2014<sup>4,18,19</sup> and 2013,<sup>12</sup> respectively, including the US Food and Drug Administration's approval of crisaborole ointment, 2%, for the treatment of mild-to-moderate atopic dermatitis and of dupilumab for the treatment of moderate-to-severe atopic dermatitis.<sup>9,10</sup> The AAAAI has recently published a multidisciplinary consensus statement regarding the current and emerging therapies for moderate-to-severe atopic dermatitis.<sup>16</sup> The statement highlights that atopic dermatitis is a systemic disease, provides a definition for moderate-to-severe disease, and recommends dupilumab as first-line systemic treatment for adults with moderate-to-severe atopic dermatitis when the disease does not respond to topical treatment.<sup>16</sup>

To make recommendations more practical, the Atopic Dermatitis Yardstick was developed (**Figure 2**).<sup>20</sup> Written to complement the treatment guidelines, the Atopic Dermatitis Yardstick includes mention of recently approved therapies such as crisaborole and dupilumab.<sup>20</sup> Crisaborole is a nonsteroidal, phosphodiesterase-4 inhibitor for the treatment of mild-to-moderate atopic dermatitis.<sup>24,25</sup> Dupilumab is a human monoclonal antibody against interleukin-4 receptor alpha for the treatment of moderate-to-severe atopic dermatitis.<sup>26</sup>

A number of anti-inflammatory agents have been approved or are currently in late-phase clinical development for the treatment of atopic dermatitis (**Table 1**).<sup>11,24-29,41</sup> The majority of novel treatments for atopic dermatitis target moderate-to-severe disease.<sup>28</sup>

As with many chronic diseases, poor adherence is a significant impediment to the successful treatment of atopic dermatitis.<sup>42,43</sup> Medication adherence can be categorized into 3 distinct phases, which include initiation (filling a prescription and starting treatment), implementation (using therapy according to directions), and persistence (continuing treatment).<sup>43,44</sup> Patient nonadherence can be intentional or unintentional, and represents obstacles such as medication cost and formulary access, and limitations such as the inability to execute the treatment plan as prescribed, perhaps as a result of age, unclear instructions, or cognitive abilities.<sup>44</sup> For example, among the real-world population of US patients with atopic dermatitis who are eligible for topical corticosteroid or topical calcineurin inhibitor treatment, the annual prescription cost per patient ranged from \$53 to \$1465.<sup>45</sup>

Adherence to topical treatments for atopic dermatitis is particularly poor, with patients vastly overestimating their adherence.<sup>42</sup> Patient adherence to the topical treatment of atopic dermatitis tends to be greatest at the start of treatment (>90%) and decreases with extended duration (approximately 30% at 8 weeks),<sup>42</sup> which is a trend for many dermatitis conditions, including psoriasis and acne.<sup>46</sup>

Poor medication adherence can also be confused with poor response to therapy, which can result in unnecessary treatment escalation.<sup>47</sup> Adherence may be better with oral medications than with topical treatment for skin disease.<sup>47</sup> Although it is generally accepted that oral medications are preferable to frequent injections, at least one study that was conducted to explore adherence to oral drugs versus injectable agents in patients with psoriasis showed greater adherence to injectable medications.<sup>48</sup>

Poor medication adherence can also result from complex treatment regimens for atopic dermatitis.<sup>49</sup> For example, atopic dermatitis regimens can include up to 3 emollient therapies (cream or ointment, bath oil, and soap substitute), 2 topical corticosteroids (eg, specific to face and body), and wet dressings. In addition, patients often must keep track of many different topical preparations, which can lead to treatment mistakes.<sup>49</sup>

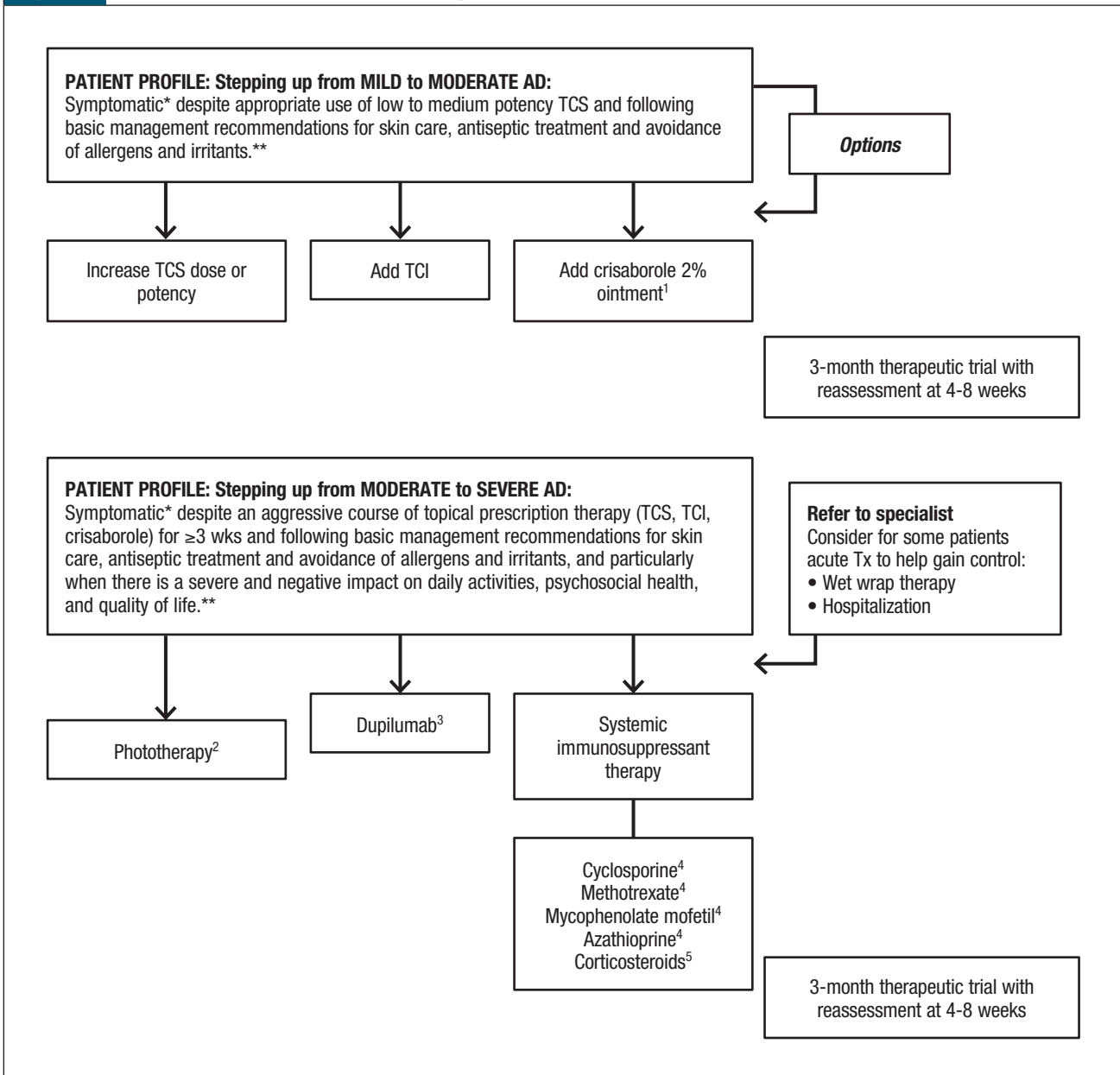
Safety concerns associated with atopic dermatitis treatments may also negatively affect treatment adherence. Steroid phobia refers to patients and caregivers' negative feelings and beliefs (from mild apprehension to irrational fear) regarding topical corticosteroid treatment.<sup>50</sup> The prevalence of steroid phobia ranges from 21% to 83.7%.<sup>50</sup> Steroid phobia has been correlated with poor adherence to treatment.<sup>51</sup> In studies of steroid phobia that identified where patients obtained information about topical corticosteroids, physicians and healthcare workers were listed as a top source, which suggests that careful counseling and education may assist in alleviating patient concerns.<sup>50</sup>

### Impact of Atopic Dermatitis on Quality of Life

Atopic dermatitis has a substantial detrimental effect on the QOL of patients and their families.<sup>5</sup> In children, the physical impact includes itching and scratching, which can result in significant sleep disturbance.<sup>5,52,53</sup> The emotional impact of atopic dermatitis in children includes behavioral problems, irritability, crying, and embarrassment.<sup>5,53</sup> Social isolation is also a serious concern.<sup>52</sup> In a comparative study of QOL in children with chronic diseases, generalized eczema was identified as the condition with the second greatest impact on QOL, exceeded only by cerebral palsy.<sup>54</sup> Atopic dermatitis reduces the QOL of families of patients with atopic dermatitis, with sleep disturbance as one of the primary domains affected.<sup>5,53</sup>



**Figure 2** Atopic Dermatitis Yardstick Flow Diagram



The patient profiles and recommendations for treatment are based on current guidelines and newer data and the authors' clinical experience as described by Boguniewicz et al.<sup>20</sup>

\*Poorly or inadequately controlled signs and symptoms of AD.

\*\*Before stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively affect response to therapy. Confirmation is needed that the increased level of symptoms is due to AD.

<sup>1</sup>Indicated for patients at least 2 years old with mild-to-moderate AD.

<sup>2</sup>The patient should be willing and able to commit to phototherapy in terms of cost, convenience, and access.

<sup>3</sup>Indicated for patients at least 18 years old with moderate-to-severe AD. It is the authors' expert opinion<sup>20</sup> that dupilumab has a safety and efficacy profile that is better than that of immunosuppressive agents or phototherapy; cost and coverage are extremely important considerations. Documentation of the patient's disease severity, prior therapies, including failures, and impact on quality of life might be required.

<sup>4</sup>Not approved by the Food and Drug Administration to treat AD.

<sup>5</sup>Approved by the Food and Drug Administration to treat AD but not recommended for long-term maintenance. A short-course of systemic corticosteroids can help resolve severe symptoms, but exacerbation at discontinuation is common. Systemic corticosteroids also can be used as cotreatment during the initiation and optimization of phototherapy, other systemic immunosuppressants, and/or dupilumab.

AD indicates atopic dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

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**Table 1** Approved and Emerging Treatments for Atopic Dermatitis

Drugs for atopic dermatitis	FDA regulatory status	Route of administration	Age-group <sup>a</sup>	Dosage(s)	Atopic dermatitis indication	Comments
<b>Approved drugs</b>						
Corticosteroids <sup>b</sup>	Approved	Topical	Infants, children, adults	Varies	All disease stages	AEs of concern include striae, skin atrophy, telangiectasia, delayed wound healing, easy bruising; pregnancy category C
		Oral			Moderate-severe	AEs of concern include insulin resistance, insomnia, adrenal gland suppression, bone metabolism; pregnancy category C
Tacrolimus <sup>29-31</sup>	Approved	Topical	Children, adults	0.03%, 0.1%	Moderate-severe: children (0.03%), adults (0.03%, 0.1%)	TCI; AEs of concern include burning with application, potential increase in risk for lymphoma <sup>c</sup> ; pregnancy category C
Pimecrolimus <sup>32</sup>	Approved	Topical	Children, adults	1%	Moderate-severe	TCI; AEs of concern include burning with application, potential increase in risk for lymphoma <sup>c</sup> ; pregnancy category C
Dupilumab <sup>26</sup>	Approved	Subcutaneous	Adults	300 mg	Moderate-severe	IL-4/IL-13 antibody; AEs of concern include conjunctivitis, nasopharyngitis, upper respiratory infection, injection site reaction, herpes infection, headache <sup>d</sup> ; pregnancy category not assigned
Crisaborole <sup>24,25</sup>	Approved	Topical	Children, adults	2%	Mild-moderate	PDE-4 inhibitor; AEs of concern include burning with application <sup>d</sup> ; pregnancy category not assigned
<b>Drugs in late-stage clinical trials</b>						
Pimecrolimus	Phase 3	Topical	Infants aged ≥3 months, children aged ≤12 years	1%	Mild-moderate	NCT00120523 <sup>33</sup>
Dupilumab	Phase 3	Subcutaneous	Infants aged ≥6 months, children	2 mg/kg, 4 mg/kg	Moderate-severe	IL-4/IL-13 antibody; NCT02407756 <sup>34</sup> ; NCT02612454
Crisaborole	Phase 3	Topical	Infants aged ≥3 months	2%	Mild-moderate	PDE-4 inhibitor; NCT03356977
Baricitinib (LY3009104)	Phase 3	Oral	Adults	2 mg <sup>e</sup> , 4 mg	Moderate-severe	JAK1/2 inhibitor; NCT02576938 <sup>35</sup> ; NCT03334435; NCT03334422 (BREEZE-AD2); NCT03334396 (BREEZE-AD1); NCT03435081 (BREEZE-AD5)
Over-the-counter investigational cream, not otherwise specified	Phase 3	Topical	Children aged ≥12 years, adults aged ≤65 years	Not specified	Moderate-severe	NCT03386032; active comparator is 0.05% desonide cream
Lyophilized bacterial lysates	Phase 3	Oral	Infants aged ≥6 months, children aged ≤7 years	3.5 mg	Moderate-severe	NCT03047954; immunostimulating preparation
IDP-124 lotion, not otherwise specified	Phase 3	Topical	Children, adults	Not specified	Moderate-severe	NCT03058783
Vitamin D	Phase 4	Oral	Infants aged ≥1 years, children aged ≤5 years	Stoss vitamin D (150,000 IU cholecalciferol), daily vitamin D (1000 IU cholecalciferol)	Moderate-severe	NCT03257215 (D-Vex Pilot study)
Tralokinumab	Phase 3	Subcutaneous	Adults	Not specified	Moderate-severe	IL-13 antibody; NCT02347176 <sup>36</sup> ; NCT03160885 (ECZTRA 2), monotherapy; NCT03363854 (ECZTRA 3), in combination with TCS; NCT03131648 (ECZTRA 1), monotherapy
PAC-14028	Phase 3	Topical	Children aged ≥12 years, adults	1.0%	Mild-moderate	Transient receptor potential vanilloid type 1 (TRPV1) antagonist; NCT02965118 (CAPTAIN-AD)
PF-04965842	Phase 3	Oral	Children aged ≥12 years	100 mg, 200 mg	Moderate-severe	JAK1 inhibitor; NCT03349060, monotherapy; NCT03422822, combined with topical medications
Fevipirant	Completed phase 2	Oral	Adults	450 mg	Moderate-severe	Prostaglandin DP <sub>2</sub> (CRTh2) receptor antagonist; NCT01785602
Q301	Completed phase 2	Topical	Adults	Not specified	Moderate-severe	Prostaglandin DP <sub>2</sub> (CRTh2) receptor antagonist; NCT02426359

**Table 1** Approved and Emerging Treatments for Atopic Dermatitis (*continued*)

Drugs for atopic dermatitis	FDA regulatory status	Route of administration	Age-group <sup>a</sup>	Dosage(s)	Atopic dermatitis indication	Comments
<b>Drugs in late-stage clinical trials</b>						
Fezakinumab	Completed phase 2	Intravenous	Adults	600-mg loading dose, 300 mg every 2 weeks	Moderate-severe	Anti-IL-22 antibody; NCT01941537 <sup>37</sup>
Lebrikizumab	Completed phase 2	Subcutaneous	Adults	125-mg single dose, 125 mg every 4 weeks, 250-mg single dose	Moderate-severe	Anti-IL-13 antibody; NCT02340234 <sup>38</sup>
Apremilast	Completed phase 2	Oral	Adults	60 mg, 80 mg	Moderate-severe	PDE-4 inhibitor; NCT02087943
				40 mg	Plaque-type	NCT00931242
Roflumilast	Completed phase 2	Topical	Adults	0.5%	Moderate	PDE-4 inhibitor; NCT01856764
Nemolizumab	Completed phase 2	Subcutaneous	Adults	0.1 mg/kg every 4 wks, 0.5 mg/kg every 4 wks, 2.0 mg/kg every 4 wks, 2 mg/kg every 8 wks	Moderate-severe	Anti-IL-31 antibody; NCT01986933 <sup>39</sup>
Ustekinumab	Completed phase 2	Subcutaneous	Adults	45 mg for patients ≤100 kg, 90 mg for patients >100 kg	Moderate-severe	IL-12/23 antibody; NCT01806662 <sup>40</sup>
				45 mg, 90 mg	Severe	NCT01945086 <sup>41</sup>
Ligelizumab	Completed phase 2	Subcutaneous	Adults	Not specified	Moderate-severe	Anti-IgE antibody; NCT01552629
Tapinarof/benvitimod/GSK2894512	Completed phase 2	Topical	Children aged ≥12 years, adults	0.5%, 1%	Moderate-severe	Aryl hydrocarbon receptor agonist; NCT02564055
Upadacitinib	Completed phase 2	Oral	Adults	7.5 mg, 15 mg, 30 mg	Moderate-severe	JAK inhibitor; NCT02925117
<p><b>NOTE:</b> Information for drugs in clinical trials can be found at <a href="http://www.ClinicalTrials.gov">www.ClinicalTrials.gov</a>.</p> <p><sup>a</sup>Age-groups are as follows, unless otherwise specified: infant, &lt;2 years; children, ≥2 years to &lt;18 years; adult, ≥18 years.</p> <p><sup>b</sup>Not all corticosteroids are approved for use in patients with atopic dermatitis; consult prescribing information before prescribing.</p> <p><sup>c</sup>Lymphoma side effect controversial.</p> <p><sup>d</sup>Limited safety data available.</p> <p><sup>e</sup>Doses tested in phase 2 studies.</p> <p>AE indicates adverse event; FDA, US Food and Drug Administration; Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; PDE, phosphodiesterase; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.</p>						

Physical and emotional domains are most affected in adults, with less impact on social functioning.<sup>5,55</sup>

The comorbidities most often associated with atopic dermatitis are related to atopy (eg, food allergies, asthma, and allergic rhinitis or allergic conjunctivitis).<sup>56,57</sup> Individuals with atopic dermatitis are at increased risk for other allergic conditions (eg, hand eczema and contact dermatitis) and cutaneous infections.<sup>56,57</sup> Increased cardiovascular risks and cancer comorbidities are also associated with atopic dermatitis.<sup>57,58</sup> Mental health comorbidities are common in patients with atopic dermatitis, with links found between the disease and attention-deficit/hyperactivity disorder, depression, anxiety, suicidal ideation, and autism.<sup>56,59</sup>

## Economic Impact of Atopic Dermatitis

Although novel therapies for atopic dermatitis provide more treatment options for patients, they also provide unique challenges for providers and payers. As previously discussed, updates to guidelines can lag behind

practice by as much as 10 years.<sup>7</sup> This places providers and payers in the position of needing to assess evolving levels of evidence for new therapies, to incorporate them within current treatment paradigms, and to take into account the cost of the therapy and distribution.<sup>60</sup>

Atopic dermatitis is associated with substantial economic burden for patients and their families, payers, and society.<sup>61</sup> **Table 2** discusses studies that show the economic impact of atopic dermatitis.<sup>45,61-67</sup> Direct costs can include prescriptions, over-the-counter treatments, physician and emergency department visits, and hospitalizations.<sup>68</sup> Individuals with atopic dermatitis use more healthcare resources than controls without atopic dermatitis.<sup>62</sup> An analysis of data from the 2013 US National Health and Wellness Survey indicated that the mean annual direct cost for an individual with atopic dermatitis is \$24,401 compared with \$14,619 for controls without atopic dermatitis (difference, \$9782; including healthcare provider visit, hospitalization, and emergency department visit costs).<sup>62</sup>

**Table 2** Economic Impact of Atopic Dermatitis

Study	Drug	Study design	Results (all in \$US)
Shrestha S et al, 2017 <sup>61</sup>	NS	HRU, insurance databases	Mean total per-patient cost (AD vs non-AD): Commercial: \$10,461 vs \$7187 Medicare: \$16,914 vs \$13,714 Medi-Cal: \$19,462 vs \$10,408 All $P < .0001$
Eckert L et al, 2018 <sup>62</sup>	NS	HRU, 2013 US National Health and Wellness Survey	Mean (SD) annual per patient costs, AD vs non-AD: Total direct: \$24,401 (\$37,355) vs \$14,619 (\$29,799) Emergency department visit: \$1459 (\$3602) vs \$608 (\$2339) Hospitalization: \$8145 (\$26,520) vs \$4759 (\$21,203) Healthcare provider visits: \$14,797 (\$19,893) vs \$9252 (\$13,882) All $P < .05$
Silverberg JL, 2015 <sup>63</sup>	NS	HRU, OOP, 2010 and 2012 National Health Interview Surveys (NHIS)	Adjusted odds ratio (95% CI) no eczema vs eczema
			OOP cost
			2010 NHIS
			2012 NHIS
			<\$1-\$499
			1.35 (1.12-1.63)
Bickers DR et al, 2006 <sup>64</sup>	NS	Direct medical costs, 2002-2003 National Ambulatory Medical Care Survey, 2002-2003 National Hospital Ambulatory Medical Care Survey, 2001 Medicare standard analytic file, 2003 Verispan Audit data and AC Nielsen OTC data	1.27 (1.05-1.54)
			\$500-\$1999
			1.65 (1.36-2.00)
			1.49 (1.22-1.81)
			\$2000-\$2999
			1.99 (1.57-2.51)
Institute for Clinical and Economic Review, 2017 <sup>65</sup>	Dupilumab, subcutaneous injection	Budget impact model, using a US health system perspective with a 3% discount rate for costs and health outcomes, 4-month cycles, and a lifetime time horizon; 2017 \$US	1.74 (1.34-2.27)
			\$3000-\$4999
			1.76 (1.35-2.30)
			2.07 (1.56-2.73)
			≥\$5000
			2.18 (1.68-2.83)
Kuznik A et al, 2017 <sup>66</sup>	Dupilumab, subcutaneous injection	Cost-effectiveness, using a US payer perspective to estimate value-based price, with costs and QALYs discounted at 3% annually	Direct cost of \$1.009 billion
Chang J and Sung J, 2005 <sup>67</sup>	Pimecrolimus cream, 1%, topical	Budget impact analysis, 2003 \$US	Average annual per-patient budget impact: \$150,000/QALY: \$38,218 \$100,000/QALY: \$29,431 \$50,000/QALY: \$20,643
			Annual dupilumab value-based price for maintenance therapy: \$150,000/QALY: \$39,941 \$100,000/QALY: \$28,769
			First year after introduction of pimecrolimus, total incremental medical and pharmacy cost of \$0.002 PMPM
Clark R et al, 2018 <sup>45</sup>	Crisaborole ointment, 2%	Budget impact analysis of TCS/TCl population <sup>a</sup> and TCl population <sup>b</sup>	TCS/TCl population: Year 1 PMPM: \$0.014 Year 2 PMPM: \$0.016 TCl population: Year 1 PMPM: -\$0.001 Year 2 PMPM: -\$0.001

<sup>a</sup>The TCS/TCl population included patients receiving a TCl or TCS alone or in combination.

<sup>b</sup>The TCl population included patients receiving a TCl alone or in combination with a TCS (excluding TCS alone).

AD indicates atopic dermatitis; CI, confidence interval; HRU, healthcare resource utilization; NS, not specified; OOP, out-of-pocket; OTC, over-the-counter; PMPM, per-member per-month; QALY, quality-adjusted life-year; SD, standard deviation; TCl, topical calcineurin inhibitor; TCS, topical corticosteroid.

The out-of-pocket costs for adults with atopic dermatitis are estimated to be from \$371 to \$489 higher than for adults without atopic dermatitis.<sup>63</sup> The indirect costs associated with atopic dermatitis include absenteeism, loss in productivity, and costs related to decreased QOL.<sup>68</sup> Individuals with atopic dermatitis report higher absenteeism, presenteeism (ie, impairment as a result of health problems while working), and overall work impairment than individuals with no atopic dermatitis.<sup>55</sup> The mean annual indirect cost for employed individuals with atopic dermatitis was \$2400 higher than for individuals without atopic dermatitis.<sup>55</sup> The most comprehensive analysis regarding the total annual burden of

atopic dermatitis in the United States identified a cost of \$4.228 billion (in 2004 US dollars).<sup>5,64</sup>

Budget impact analyses can assist with fiscal projections when new therapies come to market, and have been conducted for crisaborole and dupilumab in the United States.<sup>45,65,69</sup> The crisaborole model was developed according to guidelines from the Academy of Managed Care Pharmacy, using current topical corticosteroid and topical calcineurin inhibitor use in patients aged ≥2 years to estimate the budget impact of crisaborole over 2 years for a 1-million-member plan.<sup>45,69</sup>

Two atopic dermatitis populations were evaluated: (1) patients receiving a topical calcineurin inhibitor or



topical corticosteroid alone or in combination (combination population) and (2) patients receiving a topical calcineurin inhibitor alone or in combination with a topical corticosteroid (topical calcineurin inhibitor population, which excluded patients receiving a topical corticosteroid alone).<sup>45</sup> The total budget impact of crisaborole over 2 years in the combination population was \$350,946 (\$0.015 per health plan member, per month [PMPM]), and a decrease of \$22,871 (–\$0.001 PMPM) in the topical calcineurin inhibitor population (excluding the topical corticosteroid alone population).<sup>45</sup>

The dupilumab budget impact model was based on a cost-effectiveness model and evaluated a population with moderate-to-severe atopic dermatitis in which topical therapy was ineffective. The net cost associated with dupilumab treatment was compared with the net cost for usual care (which was assumed to include emollients but not phototherapy or systemic immunomodulatory agents).<sup>65</sup> The estimated budget impact of adding dupilumab results in an annual average increase of \$22,348 per patient treated over a 5-year time horizon.<sup>65</sup>

Cost-effectiveness analyses are often used in conjunction with budget impact analyses to help determine the clinical benefit-to-cost ratio of interventions and assist with the identification of high-benefit therapies, including treatments that affect QOL.<sup>70</sup> Using the model described above for deriving budget impact, dupilumab has estimated annual costs of \$30,516 to \$43,726 for \$100,000 to \$150,000 per quality-adjusted life-year (QALY) cost-effectiveness threshold<sup>65</sup>; the cost estimates for the same threshold were \$24,665 to \$34,946 for patients with moderate atopic dermatitis and \$38,460 to \$55,646 for patients with severe atopic dermatitis.<sup>65</sup> A separate analysis estimated the costs from the US payer perspective to be \$28,769 to \$39,941, for a threshold of \$100,000 to \$150,000 per QALY gained compared with standard of care with an annual wholesale acquisition cost of \$37,000.<sup>66</sup>

As treatment options for atopic dermatitis expand, payers must effectively manage cost and healthcare resource utilization.<sup>60,71</sup> In addition to supporting guideline-recommended approaches to therapy to maintain costs,<sup>60</sup> payers may institute programs, such as prior authorization and preferred-drug formulary status, to manage costs.<sup>60,71</sup> For example, dupilumab has paved the way for the use of biologics in the treatment of atopic dermatitis, while also introducing specialty pharmacies to the distribution channels. Previous experience with the introduction of biologics and anti-inflammatory agents for the treatment of psoriasis may assist providers and payers with adjusting to the use of new treatments for atopic dermatitis.

## Conclusion

Atopic dermatitis is a chronic disease that affects a

large proportion of the US population, and is associated with a heavy disease burden that affects patients, their families, payers, and society. The current treatment paradigm is complex, with multiple different active drugs (for various parts of the body times in the disease course, or levels of disease severity), along with moisturizers, bathing recommendations, and other lifestyle recommendations. The available treatment options for atopic dermatitis have limitations related to efficacy, tolerability, and safety concerns. The approval of 2 novel medications for atopic dermatitis within the past 2 years, and the clinical development of additional drugs, have begun to revitalize the treatment landscape for this chronic disease. ■

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## STAKEHOLDER PERSPECTIVE

### Evolving Therapies for Atopic Dermatitis Will Create New Management Challenges

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Atopic dermatitis is a chronic, pruritic inflammatory skin disease of unknown origin.<sup>1,2</sup> Atopic dermatitis often starts in infancy, but the disease also affects many adults. The National Eczema Association estimates that more than 31 million people in the United States have atopic dermatitis and that 17 million of them have moderate-to-severe disease.<sup>3</sup>

**PHYSICIANS/PATIENTS:** Recently, 2 new medications have been approved for the treatment of atopic dermatitis. Crisaborole is a topical phosphodiesterase-4 inhibitor approved for atopic dermatitis in patients aged  $\geq 2$  years, and dupilumab is an interleukin-4 receptor alpha antagonist approved for moderate-to-severe atopic dermatitis in patients aged  $\geq 12$  years.

In their article, Feldman and colleagues point out that, “The approval of these 2 novel medications for atopic dermatitis within the past 2 years, and the clinical development of additional drugs, have begun to revitalize the treatment landscape for this chronic disease.”<sup>4</sup> They also present an assessment of the economic impact of these new agents, noting that, “As treatment options for atopic dermatitis expand, payers must effectively manage cost and healthcare resource utilization.”<sup>4</sup>

This last statement becomes even more important when we look at the drug pipeline for the treatment of atopic dermatitis, which includes several monoclonal antibodies, Janus kinase inhibitors, and many other agents with novel mechanisms of action. As the choices of therapy for this disease expand, physicians and patients will face increasing complexity in rela-

tion to the choice and cost of therapy.

**PAYERS:** Payers need to develop payment and coverage policies to manage these increasing treatment choices and complexity. To do this, payers often use nationally recognized guidelines as a source for policy development. However, these guidelines can often lag behind the introduction of new agents because of the need to convene expert panels and a lack of data on the impact of new treatments in the first few months after a drug’s launch.

If the future annual cost of treating moderate-to-severe atopic dermatitis is \$30,000 or more for patients who receive biologic agents, treating only 5% (approximately 850,000) of these patients with a biologic drug can lead to an additional \$25 billion in medical cost annually. By any standard, this is a staggering number.

Indeed, the outlook for the future of patients with atopic dermatitis is bright, with increasingly effective treatments that may be tailored to an individual patient’s needs. Like most advances in medicine, however, these new treatments come at a cost that must be managed effectively in the context of limited healthcare resources. As the title of this article effectively states, these evolving treatments will create management challenges. ■

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